Declaration

February 10, 2004

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

SUPPLEMENTAL DECLARATION OF CHRISTIAN VISKOV, Ph.D.

I, Christian Viskov, Ph.D., hereby submit this supplemental declaration under Section 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (21 U.S.C. § 355(j)) and 21 C.F.R. § 10.30. It is submitted in support of that certain Citizen Petition Supplement submitted by Aventis Pharmaceuticals Inc. ("Aventis"), of even date herewith, regarding its product, Lovenox® (enoxaparin sodium) ("enoxaparin"). Aventis filed the original citizen petition on February 19, 2003 (03P-0064/CP1) (the "Citizen Petition").

I hereby declare as follows:

Background and Qualifications

1. I am currently employed by Aventis as Research Investigator, where I am in charge of Aventis Glycochemistry Unit.

2. I previously submitted a declaration in support of the Citizen Petition. My curriculum vitae is attached to that declaration as Exhibit A.

3. I received in 1993 a Ph. D in Organic Chemistry at the University of Aix-Marseille I. I am graduate in 1989 from the "Ecole Supérieure d'Ingéniere de pétroléochimie et de Synthèse Organique Industrielle", University of Aix-Marseille III (Organic Chemistry engineer).

4. I have never held a position in Department of Health and Human Services.

5. I am a member of the French Chemical Society.

6. I am an inventor on various patents and have authored or co-authored various articles on unfractionated heparin, and low molecular weight heparin. These publications are set forth in my curriculum vitae.

7. In my capacity as Research Investigator, I have become intimately familiar with Aventis' product, enoxaparin, a low molecular weight heparin ("LMWH"). From January 1997, I have acquired extensive expertise on enoxaparin, its chemical structure, and the manufacturing process used to create it from unfractionated heparin.

8. My conclusions set forth in this declaration are based upon my scientific training and experience, my extensive work in the field of LMWHs generally, and my extensive work with enoxaparin, specifically.

Discussion

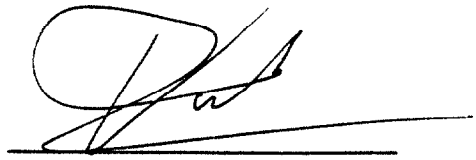
9. Presence and proportion of ATIII binding compounds in enoxaparin is a function of a specific step called depolymerization in Aventis' manufacturing process. This characteristic ATIII binding feature was demonstrated on the Enoxaparin octasaccharide fraction. There is no evidence that depolymerization occurs at the 1 position. Differences in the selectivity between positions 2 and 3 appear to be process condition dependent. At that level, three specific ATIII binding octasaccharides exist in distinct proportions. These ATIII binding compounds have different affinity for ATIII. The same phenomenon is also expected for all enoxaparin fractions above the hexasaccharides. During depolymerization, the base strength and steric hindrance as well as the reaction temperature influence the cleavage sites of unfractionated heparin chains, as well as the ratio between the resulting oligosaccharide sequences.

10. Aventis' manufacturing process creates the following three main process dependent octasaccharide sequences:

- ΔIIa-IIs-Is-Is is the result of the position 3-3 cleavage of the macromolecule model
- ΔIIa-IIs-Is-Is (1,6 anhydro) is the result of the position 3-3 cleavage, followed by 1,6 anhydro formation
- ΔIs-IIa-IIs-Is is the result of the position 2-2 cleavage

11. Aventis' manufacturing process creates some *de mimimus* batch-to batch-variation. However, this variation results only in slight changes in the *concentration* of certain structural fingerprints, not changes in the presence or absence of these fingerprints.

I declare under penalty of perjury that the foregoing is true and correct, to the best of my knowledge, information, and belief. Executed on February 10, 2004, in Vitry sur Seine.



Christian Viskov, Ph.D.